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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/751,545	01/05/2004	Otmar Klingler	DEAV2003/0002 US NP	2394

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ROSS J. OEHLER
AVENTIS PHARMACEUTICALS INC.
ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 01/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/751,545	KLINGLER ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07062004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-6 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating osteoarthritis, does not reasonably provide enablement for a method for the prophylaxis or therapy of a patient having or subject to a disease whose course involves a detrimental increase in the activity of matrix metalloproteinase 13 generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claims recite "a method for the prophylaxis or therapy of a patient having or subject to a disease whose course involves a detrimental increase in the activity of matrix metalloproteinase 13" and the specification provides that the diseases include – degenerative joint diseases, diseases of the connective tissue, periodontal diseases, wound healing disturbances, disturbances of bone metabolism, cancers, etc. The use disclosed in the specification is as matrix metalloproteinase 13 inhibitors based on the testing assay and data provided at pages 35-38, which is towards testing the MMP-13 inhibitory activity of the compounds, however, there is no nexus provided how this activity of MMP-13 inhibition correlates to method or treating all types of disorders recited in the instant claims.

First, the instant claim covers 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as metalloproteinase inhibitors, useful to treat a wide list of diseases, which include degenerative joint diseases, diseases of the connective tissue, periodontal diseases, wound healing disturbances, disturbances of bone metabolism, cancers, etc. The claimed disorders include all types of diseases, some of which have been proven to be extremely difficult to treat. It is known that MMPs play an important role in collagenoses, however, many of the MMP inhibitors have failed in clinical trials largely due to their musculo-skeletal toxicity. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as

the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area. It is inconceivable as to how the claimed compounds can treat the list of diseases recited in the claim having diverse mechanisms.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Rasmussen et al., in their article (Pharmacol. Ther., Vol. 75, 1997) stated that "Randomized clinical trials, in particular in earlier-stage disease, are required in order to fully characterize the therapeutic potential of this class of agents", see page 74, col. 1. Also, Chambers et al., in their review article (J. National Cancer Inst., Vol. 89, 1997) expressed that "Details of the mechanisms by which MMPs and their inhibitors contribute to creating an environment that favors the initiation and continued growth of primary and metastatic tumors remain to be elucidated, but are of key importance in cancer therapy". Another reference, Visse et al. (Circulation Research 2003), provides that "there are important questions that remain outstanding"; "although collagenase was the first member of the family to be discovered, the mechanism by which collagenases cleave triple-helical collagens is not understood" (see page 835). The reference further provides that "Currently, 23 MMPs and >30 ADAM metalloproteinases are known in humans, but their biological functions are not clearly understood" (see page 835). Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits.

"**Connective tissue**" is any type of biological tissue with an extensive extracellular matrix and the disorders of connective tissue include Marfan syndrome, scurvy, Ehlers-Danlos syndrome, brittle bone disease, etc. which are either genetic or environmental. Some of the diseases, e.g., brittle bone disease is treated primarily by managing fractures and promoting as much mobility and independence as possible. The state of the art provides that "Various minerals and medications have been tested throughout the years to determine if they strengthen bone in OI. Most of these substances have not been proven effective" (see http://www.oif.org/site/PageServer?pagename=GuideFor).

"**Wound healing**" consists of an orderly progression of events that reestablish the integrity of the damaged tissue. The initial wound touches off a series of programmed, separate yet interdependent responses to the injury, including inflammation, epithelialization (growth of new skin), angiogenesis (blood vessel regeneration), and the accumulation of matrix, the cells necessary to heal the tissue. Many wounds pose no challenge to the body's innate ability to heal; some wounds, however, may not heal easily either because of the severity of the wounds themselves or because of the poor state of health of the individual. The term **wound** generally refers to, and includes, any lesion that is characterized by loss of tissue, and includes but not limited to, ulcers, cuts, burns, and the like and therefore, the instant method covers a broad spectrum of events due to tissue damage. A state of the art reference, Armstrong et al., (PubMed Abstract enclosed) provides that "However, until recently, there have been no studies evaluating levels of matrix metalloproteinase or tissue inhibitors of metalloproteinase activity in chronic diabetic foot wounds".

Due to their activity of MMP-13 inhibition, the instantly claimed compounds are taught to be useful in 'a method of treating a **disturbances of bone metabolism**'. A state of the art reference, Catterall et al. (Arthritis Research and Therapy 2003), indicates that "The results from MMP inhibitors in human trials are so far disappointing because these inhibitors suffer from a range of side effects and show little effectiveness in preventing joint destruction" (see page 20).

As per the specification, the diseases of the claims include "cancers". A 'cancer' (or tumor or proliferative disorder) is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. In reference to tumor growth and metastasis, Morris et al. (Invasion Metastasis, 1997) stated that "initial arrest and extravasation may be difficult to prevent" (see the PubMed Abstract

enclosed). Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. A state of the art reference, Avgeropoulos et al. (The Oncologist 1999) provides the existence of MMP inhibitors in angiogenesis treatments, however, the reference concludes that "Malignant gliomas remain poorly understood form of cancer associated with high rates of morbidity and mortality", (see page 220).

The instant claims also recite '**prophylaxis**' and therefore, the instant claim language embraces disorders not only for the treatment, but also for "prevention" which is not remotely enabled. The MMP-13 inhibitory activity disclosed in the specification is not sufficient or competent evidence of the instant recitation of 'preventing' the various diseases encompassed by the claims. 'To prevent' actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and therefore it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "**preventive**" effect. It is inconceivable from the *in vitro* data of a small number of representative compounds can be correlated to the 'treatment and prevention' of the entire family of diseases of the claims, such that the claimed compounds can not only treat but also "prevent" all types of diseases associated with matrix metalloproteinase 13. Further, there is no evidence on record which demonstrates that the *in-vitro* screening test relied upon is recognized in the art as being reasonably predictive of success in any of the contemplated areas of 'prevention'. Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as "showing" such utility, and not "warranting further study").

The instant claims appear to be in 'reach-through' format. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification.

In the instant case, it appears that, because the instant compounds interact with MMPs and that MMPs are present in the human body, any or all disorders recited in the claims can be treated with the instant compounds for which there is no adequate written description and enabling disclosure. This is further evident from the various references discussed above, which do not provide support for 'a method of treating' the entire scope of generically embraced diseases in the instant claims.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed methods.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10 and 11 provide for the use of the compounds of claim 1, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

Claims 10 and 11 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

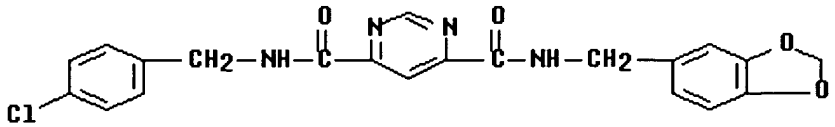
Claim Rejections - 35 USC § 102

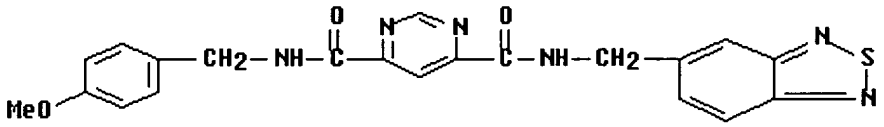
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

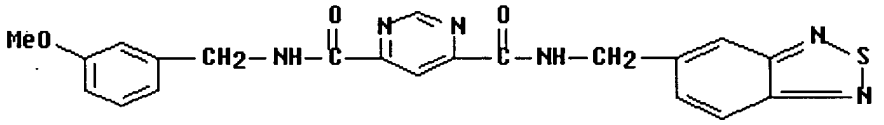
> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 and 4-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Barvian et al., WO 02/64571. The instant claims read on reference disclosed compounds, see the

compounds at page 5, lines 9-10, lines 27-28 and page 6, lines 1-2 (structures depicted below for convenience):







Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being obvious over Weithmann et al., U.S. Patent No. 6,933,298 (effective filing date February 22, 2002).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The reference teaches a generic group of pyrimidine-2,4-dicarboxylic acid diamide compounds, which embraces applicant's instantly claimed compounds. See formula I in col. 2, wherein R1-R3 can be –N(R5)-(R6) wherein wherein R5 and R6 can be independently –C(O)-(C1-C4)alkyl. The compounds are taught to be useful as matrix metalloproteinase inhibitors, see the abstract. The instant claims differ from the reference by reciting specific species or a more

limited subgenus than the reference. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. *In re Susi*, 440 F.2d 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in *Merck & Co. v. Biocraft Laboratories*, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 1-11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,933,298. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims substantially overlap the reference claims. See formula I in claim 1, wherein R1-R3 can be –N(R5)-(R6) wherein R5 and R6 can be independently –C(O)-(C1-C4)alkyl. The compounds are taught to be useful as matrix metalloproteinase inhibitors, see claims 10-17. The instant claims differ from the reference by reciting specific species or a more limited subgenus than the reference. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

2. Claims 1-11 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 10/700,273. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims substantially overlap the reference claims. The compounds are taught to be useful as matrix metalloproteinase inhibitors, see claims 6-12. The

instant claims differ from the reference by reciting specific species or a more limited subgenus than the reference. It would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as taught for the genus as a whole i.e., as therapeutic agents. One of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Receipt is acknowledged of the Information Disclosure Statement filed on July 4, 2006 and a copy is enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

January 4, 2006